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Functional Imaging of the Pancreatic Graft by Positron Emission Tomography

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Introduction: The functional status of pancreatic grafts in diabetic patients is today assessed by indirect circulating markers such as c-peptide and HbA1C. The lack of direct, non-invasive assessments of beta cell function in these sensitive grafts is an obstacle for optimized patient management. Serotonin has been associated with insulin secretion [1-2] and beta cell proliferation [3], and is not facilitated in the exocrine pancreas. We therefore posited that the serotonergic biomarker [^{11}C]5-Hydroxy-tryptophan ([^{11}C]5-HTP) could be used for functional imaging of the islets of Langerhans in the pancreatic graft by Positron Emission Tomography (PET).
Methods: Patients with variable pancreatic graft function (insulin independent, partial graft function, non-functioning grafts) were examined by 60 minutes dynamic PET/CT following intravenous administration of [^{11}C]5-HTP over the site of transplantation. Two of the patients were then examined over the native pancreas. The uptake of the radiotracer was expressed as graft-to-blood (G/B) ratio to enable within- and between-patient comparison.
Results: [^{11}C]5-HTP displayed high uptake in patients with functional pancreatic grafts (G/B_{55min} 4.3 and 5.6). In patients with failing graft function, the uptake of [^{11}C]5-HTP was conversely markedly reduced (G/B_{55min} 1.1 and 1.3). Low or negligible uptake was seen in the native non-functional pancreata. In this pilot group, there was a correlation between serotonergic facilitation as measured by [^{11}C]5-HTP-PET and graft function.
Discussion: Serotonergic facilitation as measured by [^{11}C]5-HTP-PET seems to correlate well with the functional status of the transplanted pancreas. In fact, the functional grafts had a dynamic uptake similar to that of native, healthy pancreas in non-diabetic subjects while the non-functional grafts had a dynamic uptake similar to that in pancreas in T1D subjects, indicating a correlation between transplanted beta cell function/mass and serotonergic facilitation.
Conclusion: [^{11}C]5-HTP-PET is a promising non-invasive technique for assessment of the endocrine function of the transplanted pancreas.

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Clinical Impact of Allogenic Islet Transplantation in 55 Patients under ATG Induction Therapy and Tacrolimus-MMF Maintenance Immunosuppression

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Allogeneic islet transplantation reduces glycemic variability and severe hypoglycemia in non-uremic type-1 diabetic patients maintained on immune suppression. We now report the impact of ATG-induction followed by tacrolimus and mycophenolate mofetil (MMF) on acute and chronic diabetic complications and its associated side-effects.
Data were collected during one (n=55) to five year (n=22) post-transplantation (PT). ATG dose ranged from 12.6 to 29.4 mg/kg (median 21.4), MMF was given at 1.5 gram/day (IQR 1.2 to 1.7) and tacrolimus trough levels were 9.4 ng/dl (IQR 8.8 to 10.0) during the first year and 7.2 ng/dl (IQR 6.2 to 8.2) until year 5 PT. The percentage of fasting glycemia >300 and <50 mg/dl decreased from 10 and 5% pre-transplantation respectively, to 2 ($p=0.004$) and 1% ($p<0.001$) post-transplantation. Several patients suffered from at least one hyperglycemic ketoacidosis (n=6) or hypoglycemic coma (n=25) in the year before transplantation but not in the 5 years thereafter (n=0, $p=0.02$ and n=1, $p<0.001$ resp.). No progression of micro- and macro-vascular complications was seen. Lipid profiles and blood pressure remained unchanged.
Fifty-six serious adverse events (SAEs) were reported. One patient died from cerebral hemorrhage at PT month 4 and one from liver metastasized gastric adenocarcinoma, diagnosed at PT month 27. Five patients developed CMV infections, successfully treated with intravenous (IV) ganciclovir. Most frequent SAE were gastro-intestinal infections (18/56), resolving with antibiotics and IV hydration.
Less severe adverse events were pyrosis (n=12), insomnia (n=12) and headache (n=10), occurring mainly during the first year, respiratory infections (n=23) and musculoskeletal pain (n=18) with more stable presentation. Memory impairment was seen in 6 patients, mostly with later onset. Anemia, leucopenia, neutropenia were observed in $>50\%$ of patients during the first 6 months PT, but decreased with time.
Our observations indicate that ATG-MMF–Tacrolimus regimen is safe, but is associated with expected side effects, requiring close monitoring for the occasional SAEs. The list of side effects should help select immune therapy protocols for further trials of islet transplantation.